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(54) **MICRODROPLETS OF WATER-INSOLUBLE DRUGS.**

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D scription

Microdroplets, originally called monolayer vesicles, were previously used to study the properties of the phospholipid surface as a model for the true phospholipid vesicle which, in turn, was a model for the biological membrane. This approach is to be distinguished from liposomes (multilamellar-) and unilamellar phospholipid vesicles used to deliver water-soluble drugs to the interior of cells, both *in vivo* and *in vitro*. These liposomes are true vesicles and consist of a spherical lipid bilayer with an aqueous phase inside.

Microdroplets are known and consist of spheres of organic fluid phase drug approximately 500 Angstroms in diameter and are covered with a monolayer of a suitable phospholipid.

The present invention provides a microdroplet consisting essentially of a substantially water-insoluble sphere of liquid drug substance surrounded by a phospholipid layer. The microdroplet of the invention can be defined more precisely as one of from about 20 nm (200 Ångströms) up to one µm in diameter consisting essentially of a sphere of a substantially water-insoluble drug substance dissolved in a compatible, pharmaceutically acceptable organic liquid selected from an alkane, a dialkyl ether, a long-chain ester, a hydrophobic ester, a biocompatible silicone, a biocompatible high molecular weight fluorocarbon, an oil-soluble vitamin and a volatile liquid anesthetic, the liquid plus drug being surrounded by a layer of phospholipid.

The microdroplets of the invention can be presented essentially as a timed release drug delivery vehicle composed of microdroplets consisting essentially of a substantially water-insoluble drug substance, itself a liquid or dissolved in a water-insoluble liquid, stabilized against coalescence and surrounded by a phospholipid layer.

In a further embodiment, the invention provides a process for producing microdroplets consisting essentially of a substantially water-insoluble drug substance, compatible pharmaceutically-acceptable organic liquid and a surrounding lipid layer that stabilizes the microdroplets against coalescence, said process comprising:

(1) preparing a homogenized suspension of the microdroplet components including the water-insoluble drug substance and phospholipid where the ratio of drug substance to phospholipid is sufficient to form a layer of said microdroplet and subjecting the homogenized suspension to sonification for a time sufficient to produce a cloudy, stable suspension of microdroplets; or

(2) preparing a homogenized suspension of th microdroplet comp n nts including the water-insoluble drug substance and ph spholipid, wherein th ratio of drug substance t phospholipid is sufficient t f rm a layer n said microdroplets and subjecting th homogenized suspension to high intensity mechanical agitation or shear to produce a cloudy, stable suspension of microdroplets; or

(3) dissolving the microdroplet components including the water-insoluble drug substance, organic liquid and phospholipid in an oil and water miscible organic solvent to form a solution, diluting the solution with a physiological saline solution with vigorous mechanical agitation to dissolve the solvent in the organic phase and to allow the finally dispersed constituents spontaneously to form microdroplets and removing the solvent; or

(4) preparing a homogenized suspension of the microdroplet components including the water-insoluble drug substance and phospholipid, wherein the ratio of drug substance to phospholipid is sufficient to form a layer on the microdroplet and spraying the homogenized suspension into physiological saline solution.

In a still further embodiment of the invention, there is provided the use of a normally volatile known general anaesthetic in liquid form for the manufacture of a medicament for use in producing local anaesthesia in a warm-blooded animal by injection. Further specific embodiments are characterised by the dependent claims.

The microdroplets of the invention can be used to deliver any water-insoluble/oil-soluble drug compoung via injection. Most non-polar drugs now taken orally are contemplated and are within the scope of the invention. The organic liquid phase may be the drug itself, a general anesthetic medium, fluorocarbons, vegetable oil or mineral oil. The advantages of the microdroplets provided by the invention include a relatively slow release of the drug substance to the tissues and allow for a targeted delivery by intelligent choice of the site of injection with lowered metabolic degradation, first pass effects, and toxic side-effects in the liver an the other organs.

Local anesthesia is conventionally accomplished by injection of water-soluble compounds into the site to be anesthetized. For efficacy the drugs need both hydrophobic properties, to bind to and cross cell membranes, and hydrophilic properties, to dissolve in water an diffuse to the site of action. The duration of anesthesia is limited by the fairly rapid process of absorption of the injected anesthetic into the blood. The currently-used example of a long-acting local anesthetic is bupivacaine which gives anesthesia for a few hours in some applications. There is a considerable need for a local anesthetic of longer duration, preferably of significantly longer duration. Instances of the need for longer anesthetic duration include the control of post-operative pain, relief of chronic pain in cases of pinched nerves, back pain and other applications requiring long-t rm nerve conducti n block and the like. Mang ment f long-term pain is don by analgesics, such as aspirin and pi ds, but thes ar often ineffective and sometimes give unwant d sid -effects.

In contrast to local an sthesia is general anes-

thesia, which is accomplished by inhalation of anesthetic gases to produce unconsciousness. These include nitrous oxide, halothane®, isofluoran , enfluorane and methoxyfluorane, The first-named example is a true gas; the others are volatile fluoro-chloro-hydrocarbons which exist in liquid form. Liquid general anesthetics are water-insoluble and immiscible. They are volatized in to the air which the patient breathes, they gain access to the circulation through the lungs and cause unconsciousness by binding to the nerve membranes in the brain.

The novelty of one embodiment of the invention lies in the fact that it uses general anesthetics as local anesthetics. According to a current popular conception of physicians and biomedical scientists the use of inhalation anesthetics as local anesthetics is impossible. The textbooks and scientific papers deal with the local anesthetics and the general (often termed "volatile" and "inhalation" anesthetics) as separate classes of drug substances. According to contemporary thought this division is correct since the volatile anesthetics exist as oil-like liquids which are impossible to inject due to their low solubility in water-injection as such would be unthinkable. Injection of a liquid phase of any of the volatile anesthetics would result in membrane delipidation, cellular damage and eventual tissue necrosis. Dilution of such agents in saline is not feasible because of their water-insolubility. Yet it is this low water-solubility and high solubility in the membrane phase which makes these agents effective blockers of nerve conduction in the brain (and elsewhere, but with less physiological consequence).

Brief description of the drawings

Figure 1 is a perspective representation, partially broken away, of a microdroplet of the invention containing an organic liquid and drug substance surrounded by a unimolecular lecithin outer surface;

Figure 2 is a graph based on the results of Example 1 comparing the percent response of 1% lidocaine over a period of up to 200 minutes following injection;

Figure 3 is a graph reporting the response for Example 1 as the percent response of rats to a pain stimulus induced by the tail-clamp technique, as a function of time after injection of microdroplets of methoxyfluorane;

Figure 4 is a graph based on Example 1 reporting the initial response in percent against the dose of methoxyfluorane, in volume percent; and

Figure 5 is a graph also based on Example 1 reporting the time necessary for recovery of 50% response after the injection of microdroplets of methoxyfluorane against concentration of microdroplets, in volume percent.

The uniqu ness f the invention is that a means of reducing this liquid oil-like phase to microscopic droplets, for instance approximately 500 Ångstr ms (estimated by calculation) in diameter is now available. Moreov r, these microscopic dropl ts are stabilized against coalescence by a monolayer of phospholipid. Upon intradermal injection th se microdroplets become entrapped in the interstitial space between cells and release their anesthetic in a slow and sustained manner. While not wishing to be bound to any particular theory or mode of operation, three possible mechanisms are prostulated for this: anesthetic diffusion, vesicle-cell membrane collision and fusion; see the discussion below. This is in contrast to normal elimination kinetics of an injected drug in which the drug is eliminated in a "first order" manner giving rise to an exponential decrease in concentration. With the controlled and sustained release, the concentration of the drug in the nerve and neighbouring tissue does not reach toxic concentrations. The rate of release can be controlled by the choice of anesthetic agent, based on vapor pressure and membrane solubility, and to some extent by the choice of lipid.

One skilled in the art following the instructions provided herein will have no difficulty in empirically determining an optimum relationship between anesthetic agent or water-insoluble drug substance and compatible lipid coating. For the least exchangeable agents and most non-reactive lipids, the duration of effect will be governed by the time which it takes for the microdroplets to be cleared from the interstitial space and pass into the lymphatic system. The same principles are applicable to the use of lecithin-anesthetic microdroplets as a carrier for other water-insoluble drugs such as benzocaine or dantrolene.

Local anesthesia requires delivery of the drug directly to the nerve membrane. This requires that the drug be able to bind to membranes and to traverse lipid membranes, i.e., cell membranes, and that it be water-soluble and thus able to cross the aqueous regions between cells in order to diffuse to the nerve membranes. These requirements have been fulfilled by designing local anesthetics, for example procaine and lidocaine, which have both non-polar and polar structural features. Their water-solubility results in limitation of the life-time (duration) of anesthetic effect since the local anesthetics diffuse to capillaires and are removed by the blood in the above-mentioned first order process. Theoretically, this problem could be circumvented by employing local anesthetics which are poorly soluble in water, e.g., benzocaine, but the problem then becomes the delivery of the anesthetic. Water-insoluble local anesthetics are not absorbed well through the skin and it is not possible to inject them as one injects the water-soluble ones.

As mentioned above, general anesthetics are gases and v latile liquids which ar inhaled to produc unconsciousness. Th y are po rly water-soluble compounds which enter the bloodstream by absorption in the lungs and which are carried through the bloodstr am by binding to

bl od cells and prot ins. They work on the central nervous syst m because it is most susceptible to their action, given this mode of delivery.

A microdroplet in accordance with the present invention is represented in perspective, partially broken away, in Figure 1, revealing a center containing the water-insoluble/organic phase containing the drug substance, surrounded by an outer unimolecular layer of lipid, such as lecithin. The properties of phospholipid membranes are described inter alia in my article concerning divalent cation-ligand interactions appearing in Metal-Ligand Interactions in Organic Chemistry and Biochemistry, Pullman and Goldblum, Part 2, pages 189—212, D. Reidel (1977).

One of the unique features of the invention lies in the use of volatile liquid general anesthetics to produce local anesthesia. Prior to this invention was not considered possible because it is not possible to inject an organic phase into the skin or other tissues without producing local damage due to dissolution of cell membranes and general derangement. Such a procedure would be literally unthinkable. The invention allows the injection of volatile general anesthetics without damage.

The key to accomplish the desired injection is to reduce the water-insuluble oil or anesthetic (liquid) phase to microscopic dimensions, typically by sonication, and then coat the resulting structure with a layer of a lipid. Preferred are the phospholipids, which are natural constituents of biological membranes and as such are biologically compatible. A phospholipid is chosen which exhibits repulsive interaction with the cell membranes in the target tissue such that the microdroplet remains integral for the maximum time.

As mentioned above, it is believed that the microdroplets can transfer anesthetic to the tissue and nerves by three possible mechanisms: (a) solution, (b) collision/aggregation, or (c) fusion. Comparisons of anesthetic response plotted against time in hours after injection shown in Figure 3. From this and from Figures 4 and 5 it can be deduced that the release of the anesthetic from the microdroplets is slow and sustained. Figure 3 shows that the response rats to pain stimulus induced by tail clamping is decreased by injection of 0.5 ml of 6.7% methoxyfluorane microdroplets. The initial responsiveness (t=0—2½ hrs) is also dose-dependent as shown in Figure 4. The half-time for recovery of responsiveness increases with increasing anesthetic concentration, reaching a maximum of approximately 70 hours at high concentrations as shown in Figure 5. The above are illustrative and demonstrate effectiveness using three anesthetics, variable doses at a number of sites on the rat. Lidocaine was used as a control. Durations of lidocaine anesthesia were always less than 1/10th that of preparations in accordance with the invention.

Whil the research work leading to th recognition and completi n f the present inv nti n has been conceived primarily with anesthetics, and will in large part be illustrat d and xplain d herein on that basis, the invention is n t so limit d and includes similar systems employing water-insoluble organic drug substances included in the unique drug delivery systems and pr cedures of my invention.

Microdroplet preparation

The preferred method of preparing the microdroplets of the invention is by sonication with a probe sonicator. This is described in more detail below. Alternatively, microdroplets can be prepared in a bath sonicator. For small scale preparations a 1.0 cm diameter test tube is suspended, with use of a test-tube clamp, in a bath sonicator filled with water. The components of the microdroplet (organic phase, phospholipid, physiological saline, and drug to be included) are first grossly mixed by shaking, Vortex mixing, Polytron® or other methods. The homogenized suspension is then introduced into the bath sonicator and sonicated for 1—2 hours. If the preparation is to be done on a large scale, it will be possible to omit the test tube and introduce the components of the microdroplet directly into the bath sonicator.

Microdroplets may also be produced by high intensity mechanical agitation. Useful methods include the Waring® blender, the Polytron® and high frequency shakers such as a commercial paint shaker.

An alternative method to consider is the solvent dilution method. The desired constituents of the microdroplets are dissolved at high concentration in ethanol or another oil- and water-miscible organic liquid. The ethanol solution is rapidly diluted into the physiological saline solution with vigorous mechanical agitation to insure rapid mixing. The ethanol dissolves in the aqueous phase while the other constituents cannot. The finely-dispersed constituents spontaneously form microdroplets; the ethanol can be conveniently removed by dialysis.

Microdroplets can also be formed by a process similar to spray painting. The constituents of the microdroplets are suspended and sucked into intake of a commercial spray painter and the resulting spray bubbled through a saline solution to trap the microdroplets.

By judicious choice of methods and materials the diameter of the microdroplets is controlled between approximately 50 nm (500 Ångströms) to several micrometers by controlling the method, power and lipid to organic phase ratio. Increasing the power or the ratio tends to give smaller microdroplets. If natural or unsaturated lipids are used preparation is conducted in an atmosphere free from oxygen.

Selection of organic phases

Microdroplets according to the present invention are prepared from a wide variety of organic phases which, for convenience, may be consid red by the following n n-limiting types or categori s:

1. V latile inhalati n anesthetics includ methoxyfluoran as well as hal thane, is fluorane and enfluorane.

2. Alkanes include heptane, the heptane microdroplets can incorporate benzocaine which is suitabl to produce long-duration local anesthesia. High r molecular weight alkanes will also be potent. Mineral oil as the organic phase is also of interest as it is able to carry large quantities of water-insoluble drugs. Solubility may be increased by inclusion of more polar organic compounds with the alkane phase.

3. Natural, plant-derived "oils" are also broadly contemplated, including olive oil and various vegetable oils. The "oils" are preferably screened toxicologically.

4. Ethers: Microdroplets have been made from dipropyl ether (3.4 mg/ml dimyristoyl lecithin, 6.5% n-dipropyl ether, ±4.1 mg/ml benzocaine) and dibutyl ether (5 mg/ml dimyristoyl lecithin, 7.0% n-dibutyl ether, ±4.1 mg/ml benzocaine). The dibutyl ether microdroplets and mixed dibutyl ether/chloroform microdroplets were found to have anesthetic potency. However, the anesthesia was of shorter duration (approximately ½ hour) possibly due to the greater water solubility of the dibutyl ether and chloroform which contributed to its more rapid removal. Longer-chain analogues could yield longer durations of activity.

5. Ethers: Any long-chain or hydrophobic ester is comtemplated particularly as a useful device for delivering "pro-drugs" which would be transformed into the active drug by hydrolysis by serum or cellular esterases.

6. Other organic substances which have been shown to be bio-compatible. These include by way of example silicone and high molecular weight fluorocarbons.

The organic phase selected will be fully compatible with the drug substance employed and pharmaceutically acceptable for product formulation/preparation purposes. As with all medical applications once the microdroplets are successfully prepared from a given organic phase and the selected drug substance incorporated therein, toxicological and efficacy screening is routine. Preferably the various components from which the microdroplets are made are subjected to toxicological screening as well.

Lipids

Various lipids are also suitable for use in preparing the microdroplets of the present invention. Mixtures of two or more such lipids are useful to vary the surface properties and reactivity. All of the microdroplets in the working examples reported herein are made primarily from lecithin (phosphatidylcholine). This, together with sphingomyelin which is also contemplated, constitutes Class A. In Class B, are listed the phospholipids which can also be used to make microdroplets in the pure form, but which will react with calcium in the serum to give microdroplet aggregation or binding to cell membranes. The tendency to d this can be decreased by dilution with ph s-pahtidylcholine, and thus there is a means of controlling the reactivity f the micr droplet. Class C contains only ne repr sentative, phosphatidylethanolamin . In the pur state it self-aggr gates in a calcium-independent fashion. It is expected to hav strong tendencies to aggregate with cell membranes. This tendency can be decreased by diluting it with lecithin. Class D, the steroids, do not form membranes or microdroplets by themselves, but which can be incorporated into the membrane, increasing its stability and decreasing its reactivity. Class E includes all molecules which can be accommodated in the monolayer. These are amphipathic molecules which can serve to change the nature of the monolayer surface and microdroplet reactivity.

Class A: Primary lipids (usable in pure form):
Lecithin (phosphatidylcholine)
Sphingomyelin.

Class B: These can be used in the pure form to make microdroplets (or phospholipid vesicles). They are expected to be highly reactive because of calcium-dependent aggregation. Preferably these lipids are mixed with lecithin to obtain controlled degrees of reactivity with cell membranes. Mixing in phospholipid vesicle preparations has already been demonstrated.

Phosphatidic acid
Phosphatidyl serine
Phosphatidyl inositol
Cardiolipin (diphosphatidyl glycerol)
Phosphatidyl glycerol.

Class C: Phosphatidyl enthanolamine. This can be used to make microdroplets in the pure form at pH 9; they will self-aggregate when brought to pH 7. This has been shown to be feasible in phospholipid vesicle studies. Microdroplets made from phosphatidyl ethanolamine are expected to be very reactive with cell membranes. It is suggested that this lipid can be included with the normal lecithin to increase the reactivity to cell membranes.

Class D: Steroids: These should not be used in the pure form to make microdroplets but can be mixed with lecithin or other lipids to produce a surface which is less reactive, and presumably more stable.

Cholesterol (natural constituent of membranes)

Estrogens: Estirol, estrone, estradiol and diethylstilbestrol

Androgens: Androstenedione, testosterone (the microdroplet would also constitute a delivery system for estrogens and androgens).

Class E: Semi-lipoidal molecules which can incorporate into the monolayer and change the surface activity of the microdroplet. These molecules could also be delivered to the nerve by the microdroplet.

Stearylamine or other long-chained alkyl amines which can be primary, secondary, tertiary or quaternary substituted. These give the microdroplet surface a positive charge and make them more reactive for the cell membran s. Thes compounds could also be delivered to th nerv .

Arachid nic acid r fatty acids. C uld be incorp rat d into surface giving alt red lipid packing and increas d reactivity with cell membranes.

The microdroplet is also a means of delivery of arachidonic acid for manipulations of prostaglandins.

Class F: Membrane-active agents, Nystatin, amphotericin B and gramacidin. These are surface-active antibiotics which have been shown to bind to the surfaces of phospholipid membranes and change their permeability. They are expected to change the reactivity of the microdroplet. The microdroplet is also a means of subcutaneous delivery of these antibiotics.

Several forms of lecithin are contemplated. For example lecithin is available as egg or bovine heart lecithin (natural) or in several synthetic varieties which differ in chain length. These include chain lengths ranging from 4 to 19 carbons (Supelco, Inc.). Dimyristoyl (14 carbons) and didodecanoyl (12 carbons) lecithin were used in the working examples (below). Didodecanoyl lecithin (12 carbons) may be considered more useful because the microdroplets will be more resistant to aggregation below room temperature. It is believed that lecithins with chain lengths in the biological range (10—18 carbons) are useful in various applications. Unsaturated lecithins (dioeoyl), dilinoeoyl; alpha-palmito, beta oleoyl; alpha palmitoyl beta linoleoyl and alpha oleoyl beta palmitoyl) are also available. Diarachidonyl lecithin (highly unsaturated and a prostaglandin precursor) is also available, as is alpha palmito beta myristoyl (mixed unsaturated chains) lecithin.

Phosphatidic acid is available from egg or as synthetic compounds (dimyristoyl, dipalmitoyl or distearoyl, Calbiochem). Bovine phosphatidyl serine is available (Supelco or Calbiochem).

Phosphatidyl inositol is available from plant (Supelco) or bovine (Calbiochem) sources. Cardiolipin is available (Supelco) from bovine or bacterial sources. Phospahtidyl glycerol is available from bacterial (Supelco) sources ir as synthetic compounds (dimyristoyl or dipalmitoyl; Calbiochem).

Phosphatidyl ethanolamine is available as egg, bacterial, bovine, or plasmalogen (Supelco) or as synthetic compounds dioctadecanoyl and dioleoyl analogues and dihexadecyl, dilauryl, dimyristoyl and dipalmitoyl (Supelco and Calbiochem).

Drugs

The following is a list of drug substances which may be incorporated into the microdroplets of the invention. This list is presented for purposes of illustration.

1. The volatile anesthetics are described above. They include methoxyfluorane, isofluorane, enfluorane and halothane®. Heptane was also shown to have anesthetic potency.

Th f ll wing drugs will be incorporated primarily in the organic phase of the micr dr - plet. They are all uncharged, lipophilic water-insoluble drugs which have high oil solubility. In th ir applications, the organic phases of the microdroplets are made from the organic phase demonstrating the greatest drug solubility in macroscopic tests.

2. Water-insoluble local anesthetics. At a level of 2 mg/ml benzocaine can be incorporated into a 10% heptane microdroplet suspension (8.3 mg/ml dimyristoyl lecithin).

3. Dantrolene, a direct-acting muscle relaxant, is incorporated into methoxyfluorane microdroplets, heptane or mineral oil microdroplets. The resulting microdroplet suspension is injected around muscles and nerves for control of spasticity. This could circumvent the problem of hepatic toxicity seen with chronic oral administration of the drug.

4. The barbiturates (barbituric acid, pentothal and phenobarbital have been shown to block ganglionic transmission. The hypnotic/sedatives of the benzodiazepine class (diazepam and oxazipam are presently used as muscle relaxants. These effects could be amplified by direct injection via microdroplets and the central nervous system effects obviated.

5. The microdroplet is believed to be an excellent means of direct and targeted administration of anti-inflammatory agents. Phenylbutazone can be administered at high concentration at the site of inflammation. The side-effects of nausea and vomiting, typically seen with oral administration, would be largely circumvented and much higher local doses could be used. Other anti-inflammatory or anti-arthritic agents which could be used include acetaminophen and colchicine.

6. Present evidence suggests that the rate of release of water-insoluble substances from the microdroplets to the blood stream will be slow if the microdroplets are injected intradermally or intramuscularly. This slow release is believed to be useful for the following classes of drugs:

(a) cardiovascularly active drugs: propranolol, labetalol, reserpine, nitroglycerin;

(b) hormones: estrogens, androgens, anabolic steroids in cancer chemotherapy;

(c) spironolactone (diuretic);

(d) coumarin (and other oral anti-coagulants);

(e) oil-soluble vitamins;

(f) prostaglandins and their analogues.

7. There are a number of drugs which are suitable for incorporation into microdroplets but the advantages of this treatment form with intradermal or intramuscular injection are not particularly apparent at present. These include: tricyclic anti-depressants, phenytoin (antiepileptic), and other centrally-acting agents.

All parts and percentages reported herein are by weight and all temperatures reported in degrees Celsius, unless otherwise indicated. The compositions of the invention can comprise, consist essentially of or consist of the materials set forth and the process or method can comprise, consist essentially of or consist of the steps set forth with such materials.

Detailed description of th invention

Example 1

Anesth tic-containing lecithin-coated micro-

droplet are prepared by sonication in the following manner. Dimyristoyl phosphatidylcholine (41 mg) is added to a test tube and methoxyfluorane (0.2 ml) is pipetted in. The mixture is swirled in the tube at approximately 37°C and the lipid is observed to dissolve or be suspended to a limited extent. Next, sterile physiological saline (3.0 ml) is added and the tube is suspended under a Sonifier® Cell Disrupter, Model W185D (Heat System and Ultrasonics, Plainview, New York). The microtip is inserted and the sample is sonicated gently (power stage 2) for approximately one minute until the sample is dispersed. The oil, solid and aqueous phases are not distinguishable and gross homogeneity is obtained. The result appears as a milky single phase.

Next, the power is increased to stage 4 and the sample is sonicated for a total of approximately 5 minutes. The sonication temperature is between 30° and 45°C. The temperature can be controlled either by circulation of coolant around the sonication vessel or by interrupting the sonication periodically and allowing the sample to cool. The result of the sonication is a stable, homogenous suspension of lecithin-methoxyfluorane microdroplets. At the stated concentration, the suspension appears slightly cloudy to the eye; turbidity decreases with increasing dilution of the sample in accordance with Beer's Law. Efficacy and microdroplet properties do not depend on the concentration at which the microdroplets were prepared, as observed from experiments carried out over a wide range of concentrations. The preparation is stable for several days when stored at 30°C. The preparation retains the smell of methoxyfluorane indicating that the component is there and is releasable. Control experiments in which the lecithin is omitted from the medium failed to give microdroplets; phase separation was obtained immediately.

The efficacy of the preparation was tested with laboratory rats using a tail-clamp assay according to the method of Munson et al; (Munson, E.S., Hoffman, J.C. and DiFazio, C.A. "The Effects of Acute Hypothyroidism and Hyperthyroidism on Cyclopropane Requirement (MAC) in Rats" Anesthesiology 29; 1094—1098 (1968). The anesthetic preparation was injected into the tail and injections were distributed over four sites (0.5 ml total) such that a 3—4 cm long weal was obtained, encompassing all sides of the tail. Anesthesia was determined as being either present or absent from the response of the animal to clamping of the treated area with forceps as visually observed by squeeks or rapid movement. Untreated areas of the tail served as the control for the responsiveness of the animal to pain. As additional controls, some of the animals were injected with saline or sonicated lecithin without anesthetic agents. These controls showed uniformly no effect.

The efficacy of the microdr plet preparation was compared with that of 0.5 ml of 1% lidocaine (Figure 2) and bupivacaine in separate animals treated and tested in parallel. At least f ur animals w re assigned to each treatment and dosage group. Th y w re tested immediately after treatment and at timed intervals thereafter until complete repsonsiveness was obtained in all animals.

With lidocaine, the animals were rendered 0% responsive. On the time scale presented, the effect wore off rapidly. After 2.5 hours the animals were 50% responsive and no measurable effect is observed after six hours. A similar experiment was carried out using 0.5% bupivacaine which is the longest acting local anesthetic in clinical use. A similar response was observed (data not shown), the animals became 50% responsive after 6.5 hours and there was no measurable effect after 8 hours.

The results are shown in Figure 3 which illustrates the responsiveness of the 12 animals to the pain stimulus for the lecithin-methoxyfluorane microdroplet (1.28% lecithin, 6.25% methoxyfluorane) and for 1% lidocaine. "Responsiveness" is averaged for all animals (100=full pain response in all animals; 0%=no pain response in all animals). This figure shows the responsiveness as a function of time after treatment. In the period of 1 to 2.5 hours after injection the animals were rendered 8% responsive to the pain stimulus. The effect persists during the times that the lidocaine effect had worn off (cf. Figure 2).

Half-responsiveness was observed 70 hours after injection. The effect slowly wears off, with 100% responsiveness observed after approximately 140 hours, i.e., about six days.

Figure 4 shows the dependence of the initial responsiveness as a function of the dose. Figure 5 shows that the half-time for return to 50% responsiveness and shows a sigmoidal dependence on the dose of methoxyfluorane microdroplets, reaching a maximal half-time of 70 hours. Both the initial responsiveness effects and the half-time effects depend on the microdrop concentration in a graded manner consistent with the proposed mechanism of action: Large doses create large reservoirs of anesthetic within the tissue which must be removed before responsiveness to pain stimuli can be observed. Smaller doses can be used to create marginal anesthesia for a shorter time. In the latter case the injected dose of microdroplets does not have sufficient reservoir capacity to saturate the tissue. The maximal half-time for return of responsiveness of approximately 70 hours observed at maximal dose is believed to reflect the time that it takes the vesicles to be cleared from the tissue via the lymphatics.

Example 2

Example 1 was repeated this time using 6.7% n-heptane as the anesthetic and similar results were obtained.

Exampl 3

Example 1 was r peated this time using microdroplets with a 1:1 mixture of n-dibutyl ether and chlorof rm as th organic phase (6.7%)

but the anesthesia was of short duration (1—2 hours). This correlates with the increased volatility and water solubility of these agents which give more rapid removal via th blood. The n-dibutyl ether chloroform microdroplets were shown to be effective in solubilizing benzocaine, but no increased efficacy of anesthesia was observed.

Example 4

Lecithin coated methoxyfluorane microdroplets were injected into the hind leg muscle of the rat (2.0 ml total dose) and this resulted in immobilization of its hind quarters for one day. Controlled injections of lidocaine gave only short-duration immobilization (approximately two hours).

Example 5

Microdroplets were prepared as described in Example 1 except that the organic phase consisted of 6.7% mineral oil and the phospholipid monolayer consisted of didocecanoyl (dilauryl) lecithin (12.8 mg/ml). The microdroplets were found to be stable at 37°C *in vitro* for over a month. The microdroplets were injected into the tails of two rats and no toxic effects were observed. Local anesthesia was not observed, in accordance with expectations since mineral oil lacks anesthetic potency.

Example 6

Microdroplets were prepared as described in Example 1 except that the organic phase consisted of 2.42% methoxyfluorane, 2.42% n-dibutyl ether and 1.8% mineral oil solubilizing 1.8 mg/ml benzocaine and the phospholipid monolayer consisted of didocecanoyl (dilauryl) lecithin (12.8 mg/ml). The microdroplets were found to be stable at 37°C *in vitro* for over a month. The microdroplets were injected into the tails of two rats and no toxic effects were observed. Local anesthesia was observed with kinetics similar to that given in Figures 4 and 5 for 2.4% methoxyfluorane.

Claims

1. Use of a normally volatile known general anesthetic in liquid form for the manufacture of a medicament for use in producing local anesthesia in a warm-blooded animal by injection.

2. The use according to claim 1, wherein said anesthetic is a fluoro-halo-hydrocarbon compound.

3. The use according to claim 2, wherein said fluoro-halo-hydrocarbon compound is selected from 1-bromo-1-chloro-2,2,2-trifluoroethane, 1-chloro-2,2,2,-trifluoroethyl difluoromethyl ether, 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether and 2,2-dichloro-1,2-diflu r ethyl methyl th r.

4. Th use according to claim 3, wherein said fluoro-halo-hydrocarbon comp und is 2,2-dich- l ro-1,1-difluoroethyl methyl eth r.

5. The use according t any one of claims 1 to 4, wherein said medicament is designed for injection into tissue or a body cavity.

6. The use according to claim 5, wherein said medicament is designed for intradermal injection.

7. The use according to claim 5, wherein said medicament is designed for intramuscular injection.

8. The use according to any one of the preceding claims, wherein said medicament is in emulsion form.

9. The use according to any one of claims 1 to 7, wherein said medicament is in liquid form either alone or dissolved in an organic solvent in order to form a discrete organic phase dispersed in an aqueous phase.

10. The use according to claim 9, wherein said organic phase comprises an emulsifying agent.

11. The use according to claim 10, wherein said emulsifying agent is a phospholipid.

12. A microdroplet consisting essentially of a substantially water-insoluble sphere of liquid drug substance surrounded by a phospholipid layer.

13. A microdroplet of from 20 nm (200 Ångströms) up to one µm in diameter consisting essentially of a sphere of a substantially water-insoluble drug substance dissolved in a compatible, pharmaceutically acceptable organic liquid selected from an alkane, a dialkyl ether, a long-chain ester, a hydrophobic ester, a biocompatible silicone, a biocompatible high molecular weight fluorocarbon, an oil-soluble vitamin and a volatile liquid anesthetic, the liquid plus drug being surrounded by a layer of phospholipid.

14. An injectable pharmaceutical composition comprising a microdroplet according to claim 12 or 13 together with a pharmaceutically acceptable injectable vehicle.

15. A timed release drug delivery vehicle composed of microdroplets consisting essentially of a substantially water-insoluble drug substance, itself a liquid or dissolved in a water-insoluble liquid, stabilized against coalescence and surrounded by a phospholipid layer.

16. A microdroplet according to claim 12 or 13, a composition according to claim 14 or a drug delivery vehicle according to claim 15, wherein the drug substance is a general anaesthetic in liquid form; a water-insoluble local anaesthetic; a muscle relaxant such as dantrolene; a hypnotic/sedative of the benzodiazepine class or centrally acting agents; a steroidal or non-steroidal anti-inflammatory agent; a membrane-binding lipophilic antibiotic; a cardiovascularly active drug; a hormone; an anabolic steroid as cancer therapeutic agent; a diuretic such as spironolactone; an anti-coagulant; an oil-soluble vitamin; a prostaglandin; a tricyclic anti-depressant or an anti-epileptic such as phenytoin.

17. Us of a microdroplet or c mposition or v hicle acc rding t any on f claims 12 to 15 in which the drug substance is an anaesth tic for the manufacture of a medicament f r us in inducing anesth sia at the sit at which anes-

thesia is desired.

18. A process for producing microdroplets consisting essentially of a substantially water-insoluble drug substance, compatible pharmaceutically-acceptable organic liquid and a surrounding lipid layer that stabilizes the microdroplets against coalescence, said process comprising:

(1) preparing a homogenized suspension of the microdroplet components including the water-insoluble drug substance and phospholipid where the ratio of drug substance to phospholipid is sufficient to form a layer on said microdroplet and subjecting the homogenized suspension to sonification for a time sufficient to produce a cloudy, stable suspension of microdroplets; or

(2) preparing a homogenized suspension of the microdroplet components including the water-insoluble drug substance and phospholipid, wherein the ratio of drug substance to phospholipid is sufficient to form a layer on said microdroplets and subjecting the homogenized suspension to high intensity mechanical agitation or shear to produce a cloudy, stable suspension of microdroplets; or

(3) dissolving the microdroplet components including the water-insoluble drug substance, organic liquid and phospholipid in an oil and water miscible organic solvent to form a solution, diluting the solution with a physiological saline solution with vigorous mechanical agitation to dissolve the solvent in the organic phase and to allow the finally dispersed constituents spontaneously to form microdroplets and removing the solvent; or

(4) preparing a homogenized suspension of the microdroplet components including the water-insoluble drug substance and phospholipid, wherein the ratio of drug substance to phospholipid is sufficient to form a layer on the microdroplet and spraying the homogenized suspension into physiological saline solution.

19. A process according to claim 18 in which the resulting microdroplets range from 200×10^{-8} cm to 10×10^{-4} cm in diameter.

20. A process according to claim 19 in which the resulting microdroplets are of the order of 500×10^{-8} cm in diameter.

21. A process according to any one of claims 18 to 20 in which the sonification is conducted for 1 to 2 hours.

22. A process according to any one of claims 18 to 21 in which the drug substance is a local or general anaesthetic in liquid form.

Patentansprüche

1. Verwendung eines normalerweise flüchtigen bekannten Allgemeinanästhetikums in flüssiger Form für die Herstellung eines Medikaments zur Erzeugung einer Lokalanästhesie in Warmblütern durch Injektion.

2. Verwendung nach Anspruch 1, wobei das Anästhetikum ein Fluorhalogenk hlenwasserstoff ist.

3. Verwendung nach Anspruch 2, wobei der Fluorhalogenkohlenwasserstoff unter 1-Brom-1-chlor-2,2,2-trifluorethan, 1-Chlor-2,2,2-trifluorethyldifluorm thylether, 2-Chlor-1,1,2-trifluorethyldifluormethylether und 2,2-Dichlor-1,1-difluorethylmethylether ausgewählt ist.

4. Verwendung nach Anspruch 3, wobei der Fluorhalogenkohlenwasserstoff 2,2-Dichlor-1,1-difluorethylmethylether ist.

5. Verwendung nach einem der Ansprüche 1 bis 4, wobei das Medikament zur Injektion in das Gewebe oder eine Körperhöhle bestimmt ist.

6. Verwendung nach Anspruch 5, wobei des Medikament zur intradermalen Injektion bestimmt ist.

7. Verwendung nach Anspruch 5, wobei das Medikament zur instramuskulären Injektion bestimmt ist.

8. Verwendung nach einem der vorherigen Ansprüche, wobei das Medikament in Form einer Emulsion vorliegt.

9. Verwendung nach einem der Ansprüche 1 bis 7, wobei das Medikament entweder selbst in flüssiger Form vorliegt oder in einem organischen Lösungsmittel gelöst ist, damit sich eine diskrete organische Phase bildet, die in einer wäßrigen Phase dispergiert ist.

10. Verwendung nach Anspruch 9, wobei die organische Phase ein Emulgiermittel umfaßt.

11. Verwendung nach Anspruch 10, wobei das Emulgiermittel ein Phospholipid ist.

12. Mikrotropfen, der im wesentlichen aus einem weitgehend wasserunlöslichen Kügelchen eines flüssigen Arzneimittels besteht, das durch eine Phospholipidschicht umgeben ist.

13. Mikrotropfen mit einem Durchmesser von 20 nm (200 Å) bis zu 1 µm, der im wesentlichen aus einem Kügelchen eines weitegehend wasserunlöslichen Arzneimittels besteht, das in einer kompatiblen, pharmazeutisch akzeptablen organischen Flüssigkeit gelöst ist, die unter einem Alkan, einem Dialkylether, einem langkettigen Ester, einem hydrophoben Ester, einem biokompatiblen Silikon, einem biokompatiblen hochmolekulargewichtigem Fluorkohlenstoff, einem öllöslichen Vitamin und einem flüchtigen flüssigen Anästhetikum ausgewählt ist, wobei die Flüssigkeit mit dem Arzneimittel von einer Phospholipidschicht umgeben ist.

14. Injizierbare pharmazeutische Zusammensetzung, die einen Mikrotropfen gemäß Anspruch 12 oder 13 zusammen mit einem pharmazeutisch aktzeptablen, injizierbaren Träger umfaßt.

15. Eine das Arzneimittel unter Verzögerung freisetzende Darreichungsform, die aus Mikrotropfen gebildet wird, die im wesentlichen aus einem weitegehend wasserunlöslichen Arzneimittel bestehen, das selbst eine Flüssigkeit ist oder in einem wasserunlöslichen Lösungsmittel gelöst ist, hinsichtlich des Zusammenfließens stabilisiert und von einer Phospholipidschicht umgeb n sind.

16. Mikr tropfen nach Anspruch 12 oder 13, Zusamm nsetzung nach Anspruch 14 oder eine Arzneimitteldarr ichungsf rm nach Anspruch 15,

worin das Arzneimittel ein Allgem inanästhetikum in flüssiger Form, ein wasserunlösliches Lokalanästhetikum, ein Muskelrelaxans wie Dantrolen, ein Hypnotikum/S dativum der Benzoazepinklasse oder zentralwirkende Mittel, ein steroidales oder nicht-steroidales entzündungshemmendes Mittel, ein Membran-bindendes lipophiles Antibiotikum, ein kardiovaskulär wirkendes Arzneimittel, ein Hormon, ein anabolisches Steroid als Krebsbehandlungsmittel, ein Diuretikum wie Spironolacton, ein Antikoagulans, ein öllösliches Vitamin, ein Prostaglandin, ein tricyclisches Antidepressivum oder ein Antiepileptikum wie Phenytoin ist.

17. Verwendung eines Mikrotropfens, einer Zusammensetzung oder Darreichungsform gemäß einem der Ansprüche 12 bis 15, wobei das Arzneimittel ein Anästhetikum für die Herstellung eines Medikaments ist, das zur Erzeugung einer Anästhesie an einer gewünschten Stelle Verwendung findet.

18. Verfahren zur Herstellung von Mikrotropfen, die im wesentlichen aus einem weitgehend wasserunlöslichen Arzneimittel, einer kompatiblen, pharmazeutisch akzeptablen organischen Flüssigkeit und einer umgebenden Lipidschicht, die die Mikrotropfen hinsichtlich des Zusammenfließens stabilisiert, bestehen, wobei das Verfahren umfaßt:

(1) Herstellen einer homogenisierten Suspension der Mikrotropfenkomponenten, wozu das wasserunlösliche Arzneimittel und das Phospholipid gehören, wobei das Verhältnis des Arzneimittels zum Phospholipid zur Bildung einer Schicht auf den Mikrotropfen ausreicht, und Beschallen der homogenisierten Suspension über einen Zeitraum, der ausreicht, um eine trübe, stabile Mikrotropfensuspension zu erzeugen; oder

(2) Herstellen einer homogenisierten Suspension der Mikrotropfenkomponenten, wozu das wasserunlösliche Arzneimittel und das Phospholipid gehören, wobei das Verhältnis des Arzneimittels zum Phospholipid zur Bildung einer Schicht auf den Mikrotropfen ausreicht, und äußerst intensives mechanisches 'Bewegen oder Scheren der homogenisierten Suspension, um eine trübe, stabile Mikrotropfensuspension herzustellen; oder

(3) Lösen der Mikrotropfenkomponenten, wozu das wasserunlösliche Arzneimittel, die organische Flüssigkeit und das Phospholipid gehören, in einem mit Öl und Wasser mischbaren organischen Lösungsmittel zur Bildung einer Lösung, Verdünnen der Lösung mit einer physiologischen Salzlösung unter heftigem mechanischen Bewegen, um das Lösungsmittel in der organischen Phase zu lösen und den letztendlich dispergierten Bestandteilen zu ermöglichen, spontan Mikrotropfen zu bilden, und Entfernen des Lösungsmitt ls; der

(4) Herstellen einer homogenisierten Suspension der Mikr tr pfenkompon nt n, wozu das wasserunlöslich Arzn imittel und das Phospholipid gehören, wobei das Verhältnis des Arzneimittels zum Phospholipid zur Bildung einer Schicht auf den Mikr tropfen ausreicht, und Einsprühen der homogenisierten Suspension in eine physiologische Salzlösung.

19. Verfahren nach Anspruch 18, bei dem die enstandenen Mikrotropfen einen Durchmesser von 200×10^{-8} cm bis 10×10^{-4} cm aufweisen.

20. Verfahren nach Anspruch 19, bei dem die enstandenen Mikrotropfen einen Durchmesser in der Größenordnung von 500×10^{-8} cm aufweisen.

21. Verfahren nach einem der Ansprüche 18 bis 20, bei dem die Beschallung 1 bis 2 Stunden lang durchgeführt wird.

22. Verfahren nach einem der Ansprüche 18 bis 21, bei dem das Arzneimittel ein Lokal- oder Allgemeinanästhetikum in flüssiger Form ist.

Revendications

1. Utilisation d'un anesthésiant général connu, normalement volatil, sous forme liquide, pour la fabrication d'un médicament destiné à produire une anesthésie locale par injection, chez un animal à sang chaud.

2. Utilisation selon la revendication 1, dans laquelle ledit anesthésiant est hydrocarburefluorohalogéné.

3. Utilisation selon la revendication 2, dans laquelle ledit hydrocarburefluorohalogéné est choisi parmi le 1-bromo-1-chloro-2,2,2-trifluoroéthane, le chloro-1-trifluoro-2,2,2,-éthyldifluorométhyléther, le chloro-2-trifluoro-1,1,2-éthyldifluorométhyléther et le dichloro-2,2-difluoro-1,1-éthyl-méthyléther.

4. Utilisation selon la revendication 3, dans laquelle ledit hydrocarburefluorohalogéné est le dichloro-2,2-difluoro-1,1-éthylméthyléther.

5. Utilisation selon l'une quelconque des revendications 1 à 4, dans laquelle ledit médicament est destiné à l'injection dans le tissu ou dans une cavité corporelle.

6. Utilisation selon la revendication 5, dans laquelle ledit médicament est destiné à l'injection intradermique.

7. Utilisation selon la revendication 5, dans laquelle ledit médicament est destiné à l'injection intramusculaire.

8. Utilisations selon l'une quelconque des revendications précédentes, dans laquelle ledit médicament est sous forme d'émulsion.

9. Utilisation selon l'une quelconque des revendications 1 à 7, dans laquelle ledit médicament est sous forme liquide soit seul, soit dissous dans un solvant organique, afin de former une phase organique discrète dispersée dans une phase aqueuse.

10. Utilisation selon la revendication 9, dans laquelle ladite phase organique comprend un agent émulsifiant.

11. Utilisation s lon la rev ndication 10, dans laqu lle ledit agent émulsifiant est un phosph lipid .

12. Microg uttelettes constituées principalement d'un sphère ess ntiellement ins luble

dans l'eau d'une drogue liquide entourée par une couch de phospholipide.

13. Microgouttelettes de 20 nm (200 Ångstr˜ms) à un µm de diamètre, constituées essentiellement d'une sphère formée d'une drogue essentiellement insoluble dans l'eau, dissoute dans un liquide organique pharmaceutiquement acceptable, compatible, choisi parmi un alcane, un dialkyléther, un ester à longue chaîne, un ester hydrophobe, un silicone biocompatible, un fluorocarbure, de haut poids moléculaire biocompatible, une vitamine oléosoluble et un anesthésiant liquide volatil, le liquide plus le médicament étant entourés par un couche de phospholipide.

14. Composition pharmaceutique injectable, comprenant une microgouttelette selon la revendication 12 ou 13, conjoinement avec un véhicule injectable pharmaceutiquement acceptable.

15. Véhicule pour la libération contrôlée d'un médicament constitué de microgouttelettes consistant essentiellement en une drogue essentiellement insoluble dans l'eau, liquide elle-même ou dissoute dans un liquide insoluble dans l'eau, stabilisée contre la coalescence et entourée par une couche de phospholipide.

16. Microgouttelettes selon la revendication 12 ou 13, composition selon la revendication 14 ou véhicule pour la libération d'un médicament selon la revendication 15, où la drogue est un anesthésiant général sous forme liquide; un anesthésiant local insoluble dans l'eau; un relaxant musculaire tel que le dantrolène; un sédatif hypnotique de la classe des benzoazépines ou des agents à action centrale; un agent anti-inflammatoire stéroïdique ou non stéroïdique; un antibiotique lipophile liant la membrane; un médicament à activité cardiovasculaire; une hormone; un stéroïde anabolisant comme agent detraitement du cancer; un diurétique tel que la spironolactone; un agent anticoagulant; une vitamine oléosoluble; une prostaglandine; un agent antidépresseur tricyclique ou un agent antiépileptique tel que la phénytoïne.

17. Utilisation d'une microgouttelette ou d'une composition ou d'un véhicule selon l'une quelconque des revendications 12 à 15, où la drogue est un anesthésiant pour la fabrication d'un médicament destiné à induire une anesthésie sur le site ou l'anesthésie est souhaitée.

18. Procédé de production de microgouttelettes consistant essentiellement en une drogue essentiellement insoluble dans l'eau, un liquide organique pharmaceutiquement acceptable, compatible, et une couche de lipide enveloppant qui stabilis les microgouttelettes vis-à-vis de la coal sc nce, ledit procéd´ consistant:

(1) à préparer une suspension homogénéisée des composants des microgouttelettes comprenant la drogue insoluble dans l'eau et le phospholipide, où le rapport de la drogue au phospholipide est suffisant pour former une couche sur lesdites microgouttelettes, at à soumettre la suspension homogénéisée à une sonification pendant une durée suffisante pour produire une suspension trouble, stable, de microgouttelettes; ou

(2) à préparer une suspension homogénéisée des composants des microgouttelettes comprenant la drogue insoluble dans l'eau et un phospholipide, où le rapport de la drogue au phospholipide est suffisant pour former une couche sur lesdits microgouttelettes, et à soumettre la suspension homogénéisée à une agitation ou un cisaillement mécanique très intense pour produire une suspension trouble, stable, de microgouttelettes; ou

(3) à dissoudre les composants des microgouttelettes comprenant la drogue insoluble dans l'eau, le liquide organique et le phospholipide, dans une huile et un solvant organique miscible à l'eau, pour former une solution, à diluer la solution avec une solution saline physiologique, sous agitation mécanique vigoureuse, pour dissoudre le solvant dans la phase organique et permettre aux constituants finalement dispersés de former spontanément des microgouttelettes, et à éliminer le solvant; ou

(4) à préparer une suspension homogénéisée des composants des microgouttelettes, comprenant la drogue insoluble dans l'eau et le phospholipide, où le rapport de la drogue au phospholipide est suffisant pour former une couche sur les microgouttelettes et pulvériser la suspension homogénéisée dans la solution saline physiologique.

19. Procédé selon la revendication 18, dans lequel les microgouttelettes résultantes sont dans la gamme de 200×10^{-8} cm à 10×10^{-4} cm de diamètre.

20. Procédé selon la revendication 19, dans lequel les microgouttelettes résultantes sont de l'ordre de 500×10^{-8} cm de diamètre.

21. Procédé selon l'une quelconque des revendications 18 à 20, dans lequel la sonification est conduite pendant 1 à 2 heures.

22. Procédé selon l'une quelconque des revendications 18 à 21, dans lequel la drogue est un anesthésiant local ou géneral sous forme liquide.

FIG. 1

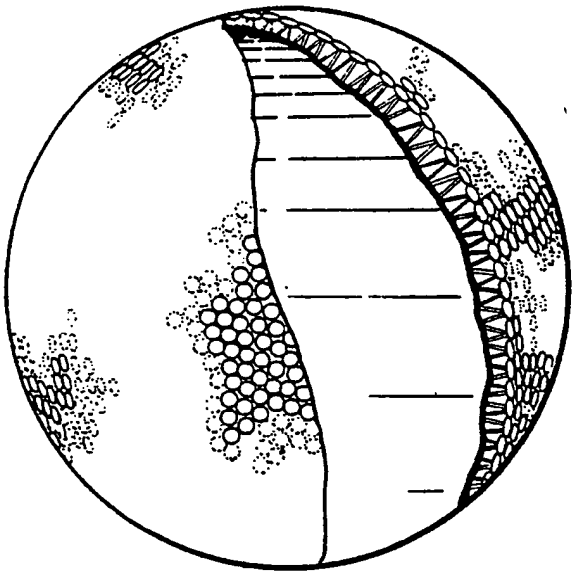


FIG. 2

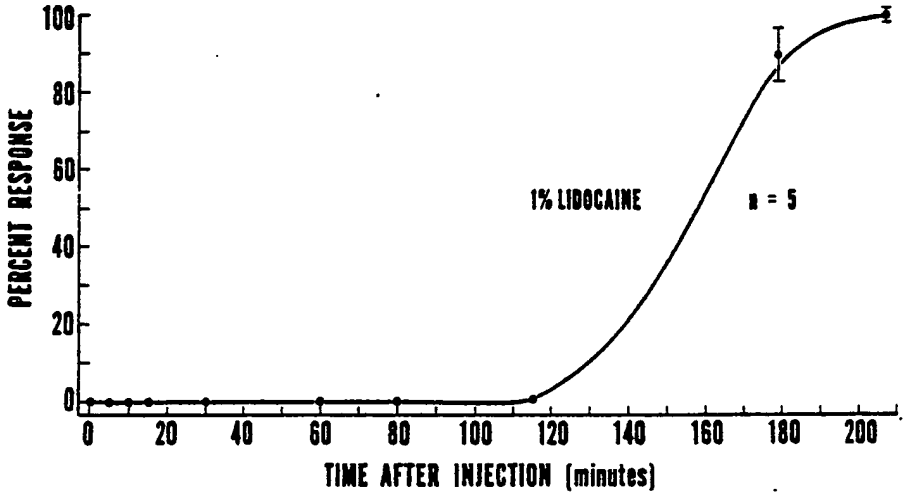

100
80
60
40
20
0
PERCENT RESPONSE
1% LIDOCAINE
n = 5
0
20
40
60
80
100
120
140
160
180
200
TIME AFTER INJECTION (minutes)

FIG.3

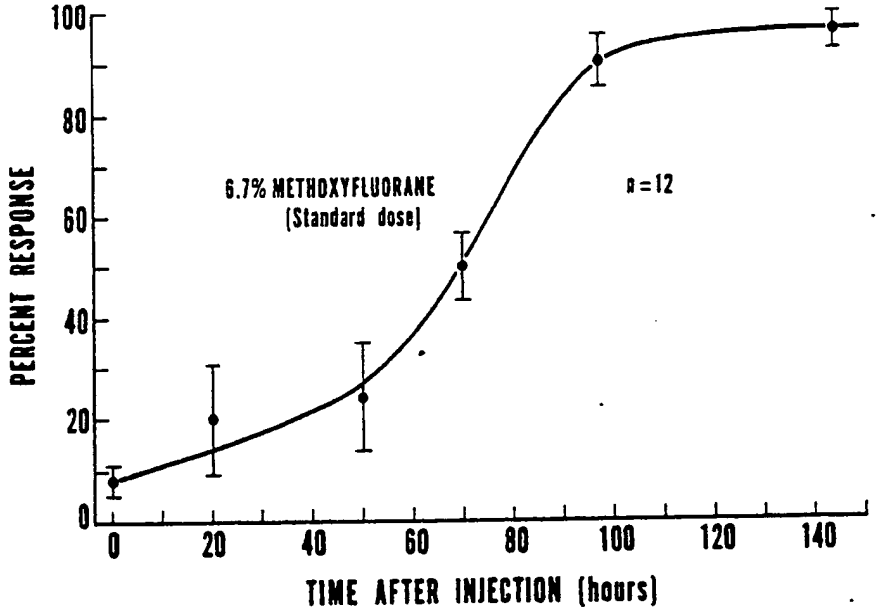

PERCENT RESPONSE
100
80
60
40
20
0
6.7% METHOXYFLUORANE
(Standard dose)
n=12
0
20
40
60
80
100
120
140
TIME AFTER INJECTION (hours)

FIG.4

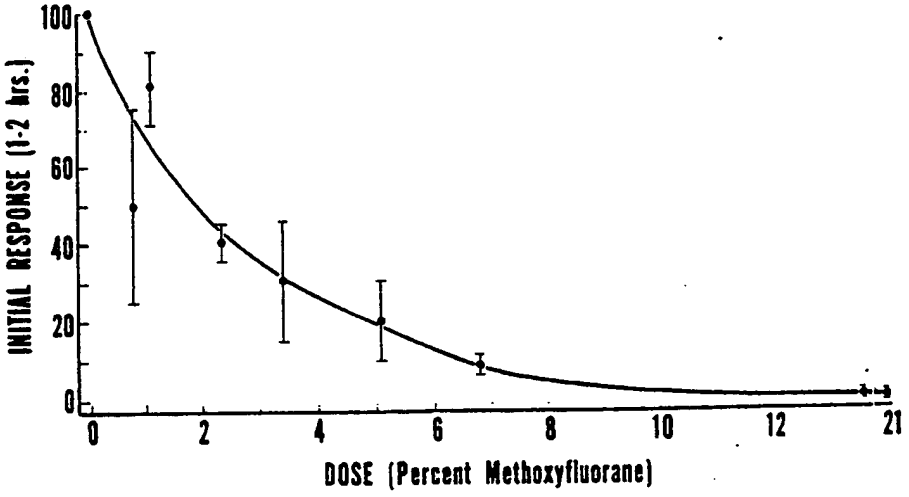
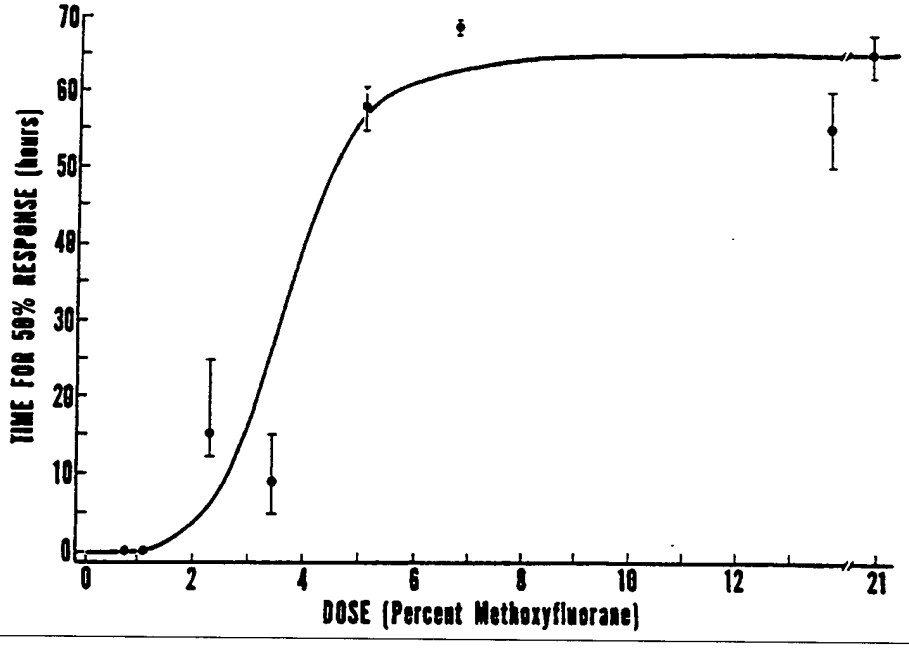

INITIAL RESPONSE (1-2 hrs.)
100
80
60
40
20
0
0
2
4
6
8
10
12
21
DOSE (Percent Methoxyfluorane)

FIG.5


TIME FOR 50% RESPONSE (hours)
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
21
DOSE (Percent Methoxyfluorane)